Paper No. 22

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte RALPH H. WEICHSELBAUM,
DENNIS E. HALLAHAN,
DONALD W. KUFE and
VIKAS P. SUKHATME

Appeal No. 1999-1365
Application No. 08/289,290

ON BRIEF

Before WINTERS, LORIN, and SCHEINER, Administrative Patent Judges.

LORIN, Administrative Patent Judge.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 from the final rejection of claims 1-3, 6, 8-14, 17-22 and 26-36, all the claims pending in the application.[1]

[1] Pursuant to 35 U.S.C. § 6(b), we review the adverse decision of the examiner. In doing so, we have considered the record, including:

- Final Rejection (paper no. 11);
- Brief (paper no. 13);
- Examiner's Answer (paper no. 16).

Claims 1, 12, 18, 26, 29, 31, 35 and 36 are illustrative of the claims on appeal and read as follows:

1. A process of treating a human cancer patient comprising providing to a cancer cell in said patient a gene encoding a radiosensitizing polypeptide operatively linked to a constitutive promoter and contacting said cell with ionizing radiation, whereby the gene is expressed and the cancer is treated.

12. A process of sensitizing a cell to the effects of ionizing radiation comprising transfecting the cell with an adenovirus vector construct comprising a gene that encodes a cytokine, wherein said cytokine is synthesized in and secreted from said cell.

18. A process of radioprotecting a cell from the effects of ionizing radiation comprising:

(a) obtaining a genetic construct comprising a gene encoding a cell radioprotecting factor operatively linked to a constitutive promoter; and

(b) transfecting the cell with the genetic construct;

whereby said radioprotecting factor is expressed and said cell is protected from said effects.

26. A process of radioprotecting a cell from the effects of ionizing radiation comprising transfecting the cell with an adenovirus vector construct comprising a gene encoding a radioprotecting factor in a mammalian cell.

29. A pharmaceutical composition comprising a genetic construct comprising a gene that encodes a cell radiosensitizing or radioprotecting factor operatively linked to a constitutive promoter dispersed in a pharmacologically acceptable carrier.

31. A method of increasing the level of a radioprotecting or radiosensitizing factor in a mammal comprising administering to the mammal an effective amount of the pharmaceutical composition of claim 29 or claim 30.

35. A process of inhibiting growth of a tumor comprising the steps of:

(a) delivering to said tumor a therapeutically effective amount of a DNA molecule comprising a constitutive promoter operatively linked to a region encoding a polypeptide having the ability to inhibit growth of a tumor cell, which coding region further is operatively linked to a transcription-terminating region, whereby said polypeptide is expressed; and

(b) exposing said cell to an effective dose of ionizing radiation.

36. A method of assessing the response of a cell to the constitutive production of radiosensitizing or radioprotecting factors following ionizing radiation, comprising:

(a) growing the cell in culture;

(b) transfecting the cell with a genetic construct comprising a gene that encodes the cell radiosensitizing factor or radioprotecting factor operatively linked to a constitutive promoter, whereby said polypeptide is expressed;

(c) exposing the cell to an effective dose of ionizing radiation; and

(d) assessing the response of said cell.

The references relied upon by the examiner are:

- Felgner et al. [Felgner] U.S. 5,264,618 November 23, 1993
- Vile et al. [Vile], "In vitro and In vivo Targeting of Gene Expression in Melanoma Cells," Cancer Research, vol. 53, March 1, 1993, pp. 962-967.
- Breakeland et al. [Breakeland], "Herpes Simplex Virus For Gene Delivery To Neurons," The New Biologist, vol. 3, no. 3, March 1991, pp. 203-218.
- Arai et al. [Arai], Cytokines: Coordinators of Immune and Inflammatory Responses," Annual Review of Biochemistry, vol. 59, 1990, pp. 783-785.
- Mattern et al. [Mattern], "Human tumor xenografts as model for drug testing," Cancer and Metastasis Reviews, vol. 7, 1988, pp. 263-284.
- Hallahan et al. [Hallahan I], "The Interaction Between Recombinant Human Tumor Necrosis Factor and Radiation In 13 Human Tumor Cell Lines," International Journal of Radiation Oncology Biology Physics, vol. 19, 1990, pp. 69-74.
- Hallahan et al. [Hallahan II], "Phase I Dose Escalation Study Of Tumor Necrosis Factor And Radiation," International Journal of Radiation Oncology Biology Physics, vol. 27, supplement 1, 1993, p. 184.
- Teng et al. [Teng], "Long-term inhibition of tumor growth by tumor necrosis factor in the absence of cachexia or T-cell immunity," Proceedings of the National Academy of Sciences, USA, vol. 88, May 1991, pp. 3535-3539.
- Neta et al. [Neta], "Radioprotection with Cytokines - Learning from Nature to Cope with Radiation Damage," Cancer Cells, vol. 3, no. 10, October 1991, pp. 391-396.
- Herz et al. [Herz], "Adenovirus-mediated transfer of low density lipoprotein receptor gene acutely accelerates cholesterol clearance in normal mice," Proceedings of the National Academy of Sciences, USA, vol. 90, April 1993, pp. 2812-2816.

The rejections are :

1. Claims 1, 3, 6, 8-14, 17-22 and 26-30 and 35 stand rejected under the first paragraph of 35 U.S.C. § 112 (enablement).

2. Claims 1-3, 6, 17, 18, 29, 31, 33, 35 and 36 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Hallahan I in view of Teng, Neta and Vile.

3. Claims 8, 9, 19 and 20 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Hallahan I in view of Teng, Neta and Vile as applied to claims 1-3, 6, 17, 18, 29, 31, 33, 35 and 36 and further in view of Flegner.

4. Claims 8, 10, 12-14, 19, 21, 26-28, 30 and 32 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Hallahan I in view of Teng, Neta and Vile as applied to claims 1-3, 6, 17, 18, 29, 31, 33, 35 and 36 and further in view of Herz.

5. Claims 8, 11, 19, 22, 30 and 32 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Hallahan I in view of Teng, Neta and Vile as applied to claims 1-3, 6, 17, 18, 29, 31, 33, 35 and 36 and further in view of Breakeland.

6. Claim 34 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Hallahan I in view of Teng, Neta and Vile as applied to claims 1-3, 6, 17, 18, 29, 31, 33, 35 and 36 and further in view of Mattern.

7. Claims 1-3, 6, 17, 18, 29, 31 and 33-35 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Hallahan II in view of Teng and Vile.

8. Claims 8, 9, 19 and 20 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Hallahan II in view of Teng and Vile as applied to claims 1-3, 6, 17, 18, 29, 31 and 33-35 and further in view of Felgner.

9. Claims 8, 10, 12-14, 19, 21, 26-28, 30 and 32 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Hallahan II in view of Teng and Vile as applied to claims 1-3, 6, 17, 18, 29, 31 and 33-35 and further in view of Herz.

10. Claims 8, 11, 19, 22, 30 and 32 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Hallahan II in view of Teng and Vile as applied to claims 1-3, 6, 17, 18, 29, 31 and 33-35 and further in view of Breakeland.

DISCUSSION

Enablement

Claims 1, 3, 6, 8-14, 17-22 and 26-30 and 35[2] are finally rejected under the first paragraph of 35 U.S.C. § 112 as being based on a non-enabling disclosure. After reading examiner's position[3], it is evident that examiner rejects the claims on the grounds that the disclosure is not enabling for the claimed invention as broadly as it is claimed.

The initial burden of providing reasons why a supporting disclosure does not enable the claims rests with the examiner. In re Marzocchi, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971). The examiner must establish that appellants have not provided sufficient disclosure, either through illustrative

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[2] Claim 2 was originally included in the rejection but has since been withdrawn (see examiner's answer, p. 15) on the grounds that, unlike the other claims, claim 2 is narrowly directed to TNF.

[3] "Claims 1, 3, 6, 8-14, 17-22, 26-30 and 35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods utilizing the tumor necrosis factor (TNF)-encoding gene, does not reasonably provide enablement for methods utilizing genes encoding any and all radiosensitizing and radioprotecting polypeptides. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The specification does not adequately teach how to use *in vivo* methods requiring expression of genes other than the tumor necrosis factor α (TNF) gene, or pharmaceutical compositions comprising other genes. Most cytokines have pleiotropic effects; they interact with each other and with various biochemical pathways (Arai et al., p. 785). One skilled in the art can not predict the outcome of expressing any and all cytokines in a mammal, because the intact animal is much more complicated than *in vitro* systems. The specification does not adequately teach which cytokines will have protective effects or which will have sensitizing effects. The systemic effects of expressing any cytokine are unpredictable, particularly if expression is not confined to any particular location.

"For the reasons discussed above, it would require [sic: have required] undue experimentation for one skilled in the art to make and use the full scope of the claimed invention. This is particularly true given the breadth of the claims, the amount of experimentation necessary, the nature of the invention, the state of the prior art, the scarcity of guidance regarding non-exemplified embodiments, and the unpredictable nature of the art." Examiner's Answer, pp. 5-6.

examples or terminology, for one skilled in the art to practice the invention as broadly as claimed without having to resort to undue experimentation. See In re Vaeck, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991).

In considering this issue, we note that appellants are not required to disclose every parameter encompassed by the claims. See In re Angstadt, 537 F.2d 498, 503, 190 USPQ 214, 218 (CCPA 1976). Furthermore, while some experimentation may be necessary, that does not preclude enablement; what is required is that the amount of experimentation "must not be unduly extensive." Atlas Powder Co. v. E.I. DuPont de Nemours & Co., 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984). Here, we can find no persuasive reasoning why the specification does not reasonably enable one skilled in the art to practice the invention as broadly as it is claimed and without undue experimentation and therefore find that examiner has not met the burden of establishing a prima facie case of nonenablement. See In re Marzocchi, 439 F.2d at 223-24, 169 USPQ at 369-70 (CCPA 1971).

Examiner (Examiner's Answer, p. 5) argues that the specification is nonenabling for the claimed invention as broadly as it is claimed because it does not

1. "provide enablement for methods utilizing genes encoding any and all radiosensitizing and radioprotecting polypeptides," except for the tumor necrosis factor (TNF)-encoding gene;

2. "teach how to use *in vivo* methods requiring expression of genes other than the [TNF] gene;" and,

3. "adequately teach which cytokines will have protective effects or which will have the sensitizing effects."

There is no dispute that the specification is enabling for the claimed invention as it applies to using the tumor necrosis factor gene. The specification (pp. 28-53) is replete with experiments and explanations of how to conduct and practice the claimed invention as it relates to employing the TNF gene, including with respect to *in vivo* tumor control (see p. 47). Furthermore, the specification (pp. 6-7) indicates that the invention covers genes for encoding other radiosensitizing and radioprotecting polypeptides.

> In one preferred embodiment, an encoding region encodes a single polypeptide. A preferred polypeptide encoded by such an encoding region is a radiosensitizing factor that has the ability to inhibit the growth of a cell and, particularly a tumor cell.
>
> An exemplary and preferred polypeptide is a cytokine, and more particularly, TNF-α, or IL-1. Other polypeptides that are within the scope of the invention include, but are not limited to a dominant negative or a tumor suppressing factor such as p53, the retinoblastoma gene product, or the Wilms' tumor gene product.
>
> Another preferred polypeptide encoded by such an encoding region has radioprotective activity toward normal tissue. An exemplary and preferred such polypeptide having radioprotective activity is interleukin-1, TNF, bFGF, interleukin-6, a free radical scavenger (MnSOD) or tissue growth factor receptor.
>
> A further preferred polypeptide encoded by such an encoding region has the ability to catalyze the conversion of a pro-drug to a drug. Exemplary and preferred such polypeptides are herpes simplex virus thymidine kinase and a cytosine deaminase.

The specification names genes, other than TNF, for encoding other radiosensitizing and radioprotecting polypeptides covered by the claimed invention and explains the types of genes that are encompassed by the claimed invention. Therefore, contrary to examiner's suggestion that no other genes are specifically suggested for use in the claimed invention, the specification is not devoid of disclosure of using genes other than the TNF gene. Other genes exist and guidance is provided to one of ordinary skill to select the appropriate genes. Furthermore, the specification suggests applying the techniques that are disclosed with reference to the TNF gene to these other candidate genes. The issue therefore is whether one of ordinary skill in the art, given the disclosure of the techniques used with the TNF gene and the knowledge of the art of making gene constructs and transfection, would be enabled to make and use the claimed invention with these other candidate genes in any environment without undue experimentation.

All that we are provided on the issue of whether undue experimentation would be required to make and use the invention as broadly as it is claimed is examiner's assertion that the "systemic effects of expressing any cytokine are unpredictable, particularly if expression is not confined to any particular location" (Examiner's Answer, p. 5). Examiner also states that undue experimentation is required because of "the breadth of the claims, the amount of experimentation necessary, the nature of the invention, the state of the prior art, the scarcity of guidance regarding non-exemplified embodiments, and the unpredictable nature

of the art" (Examiner's Answer, p 6). Examiner's position rests on the rubric that genes behave unpredictably but no fact finding has been done by the examiner to support this assertion with respect to the claimed genes encoding for radiosensitizing and radioprotecting polypeptides.

> It is true that, for instance, unpredictability is a factor to be considered. In unpredictable art areas, this court has refused to find broad generic claims enabled by specifications that demonstrate the enablement of only one or a few embodiments and do not demonstrate with reasonable specificity how to make and use other potential embodiments across the full scope of the claim.

PPG Indus., Inc. v. Guardian Indus. Corp., 75 F.3d 1558, 1564, 37 USPQ2d 1618, 1623 (Fed. Cir. 1996).

However, the burden rests initially with the examiner to substantiate unpredictability of the art and that, given the unpredictability, the specification does not provide sufficient information to guide those skilled to make and use the claimed process across the full scope of the claims. Here a clear goal is disclosed: i.e., to sensitize tumor cells to the effects of ionizing radiation or to protect nontumor cells from radiation exposure. Examples are provided which extensively describe techniques necessary to make the claimed recombinant construct (albeit with TNF, see e.g., Example IV, p. 37) and to use it in a transfection procedure. Also, other potential candidate genes are mentioned. While the specification focuses on TNF, there is no evidence that the process detailed therein for TNF is not a sufficient guide for one of skill to apply the same techniques to constructs and cells involving genes encoding other radiosensitizing and radioprotecting polypeptides. Whatever unpredictability

surrounds the use of the claimed genes in constructs and for transfecting cells to treat cancer, the need for undue experimentation appears to be mitigated by appellants' clearly described experiments of how to make and use the claimed invention with the TNF gene. There is no evidence to refute the statements made in the specification that the invention exemplified therein finds equal application in numerous other embodiments (see supra). The lack of evidence of undue experimentation as to these other embodiments cannot be replaced by speculating about the possibility of producing an inoperative result. The examiner has not met the burden of providing evidence or reasoning sufficient to support a legal conclusion of lack of enablement for the subject matter claimed. Accordingly, we reverse the enablement rejection.

Obviousness

There are seven independent claims: claims 1, 12, 18, 26, 29, 35 and 36. Claim 29 is directed to a composition; the other claims are directed to processes. Nine rejections have been made. All the claims are rejected over at least Hallahan I in view of Teng, Neta and Vile or Hallahan II in view of Teng and Vile. For reasons we discuss in the following section entitled Vacate and Remand, we vacate the rejections as they apply to claims 29 and 30 and remand the application for clarification of examiner's position as to the patentability of composition claims 29 and 30. For the following reasons, we reverse the

rejections as they apply to process claims 1, 3, 6, 8-14, 17-22 and 26-28 and 31-36.

Hallahan I in view of Teng, Neta and Vile

Examiner argues that Hallahan I discloses that "TNF and ionizing radiation act synergistically to kill human tumor cells *in vitro*" (Examiner's Answer, p. 6). Examiner admits that the reference does not teach transfecting a cell with a construct comprising the TNF gene and contacting the cell with ionizing radiation whereby the gene is expressed and the cancer is treated or nontumor cells protected. To overcome the lack of teaching to transfect a cell with TNF, examiner cites Teng, Neta and Vile. Regarding Teng and Vile, examiner (Examiner's Answer, p. 6-7) states that:

> Teng et al. disclose experiments in which murine tumor cells were transfected with the human TNF gene under control of the CMV intermediate early promoter, then implanted into nude mice (entire document). Teng et al. show that transfected tumor cell lines which produce moderate levels of TNF grow more slowly than non-transfected cell lines when implanted, and that this level of TNF production does not cause serious weight loss (e.g. Table 1). Neta et al. teach that TNF can simultaneously radiosensitize tumor cells and radioprotect normal cells (pp. 391-392; p. 394, col. 2). Other citokines such as IL-1 are reported to have similar effects. Vile et al. teach a method for transfecting tumor cells and surrounding normal cells *in vivo* by direct injection of DNA into a tumor (pp. 965-966).

As a result, examiner (Examiner's Answer, pp. 7-8) concludes:

> It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the tumor cell killing method of Hallahan et al. by transfecting tumor cells with the TNF gene as taught by Teng et al. rather than administering TNF directly. One of ordinary skill in the art would have expected that normal cells would be radioprotected by this method, given the teachings of Neta et al. and the knowledge that the DNA injection

method of Vile et al. would transfect adjacent normal cells as well as tumor cells. There would have been a reasonable expectation of success, given that TNF produced by a transfected tumor can suppress tumor growth without causing severe systemic side effects, as taught by Teng et al. ... Thus, the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Notwithstanding examiner's conclusion, for the following reasons, we find that examiner has not met his initial burden of establishing a prima facie case of obviousness. In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992).

All the claims involve using a gene construct either with a constitutive promoter or an adenovirus vector and introducing the construct to a cell. Unlike the other claims which are specifically directed to "transfecting" a cell, claims 1 and 35 call for "providing" and "delivering" the construct to the cell, respectively. In light of the disclosure which uses these terms in the same context as transfecting a cell, we interpret these claims as equally directed to introducing the construct to the cells.[4] We note that examiner has not addressed this distinction in terms and therefore we presume examiner construed these terms similarly.

Examiner admits that Hallahan does not teach transfection but relies on Teng, Neta and Vile to make the case that transfection is an alternative to Hallahan I's adding of TNF to a medium containing cells. Even if we were to find

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[4] See, for example, p. 8 of the specification: "By 'transfection,' of a cell, it is meant to introduce cloned DNA or recombinant vectors into mammalian cells. Examples of transfection procedures include ... liposomes..." Compare with p. 7: "... utilizing a viral or liposomal transfer means to deliver the construct to target cells..."

that Hallahan I with Teng, Neta and Vile would have suggested to those of ordinary skill in the art that that transfection rather than addition of TNF cells are equivalent alternatives, to establish the prima facie case of obviousness, the prior art would have to also reveal that, in so including the promoter, those of ordinary skill would have had a reasonable expectation of success in obtaining a transfected cell able to treat a human cancer patient (claim 1), sensitize a cell to the effects of ionizing radiation (claim 12), radioprotect a cell from the effects of ionizing radiation (claims 18 and 26), inhibit the growth of a tumor (claim 35) and assess the response of a cell to the constitutive production of radiosensitizing or radioprotecting factors following ionizing radiation (claim 36). "Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure." In re Vaeck, 947 F. 2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991).[5] The burden rests on the examiner to support the prima facie case of obviousness with a further showing that in introducing the constructs to the cells there would have been a reasonable expectation of success in obtaining the claimed effects. Here that has not been done.

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[5] "Where claimed subject matter has been rejected as obvious in view of a combination of prior art references, a proper analysis under § 103 requires, inter alia, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. See In re Dow Chemical Co., 837 F.2d 469, 473, 5

Although examiner makes the case that each of the claimed elements are known in the art, examiner does not show that the behavior of the genes in constructs introduced to cells behave the same as genes added to a medium containing the cells. In fact, examiner (Examiner's Answer, p. 6) states that Teng shows "that transfected tumor cell lines which produce moderate levels of TNF grow more slowly than non-transfected cell lines when implanted." This suggests to us that the behavior of transfected and nontransfected cells with radioprotecting/radiosensitizing genes is not the same and therefore the ultimate result is a matter of speculation. Accordingly, we do not find that examiner has established a reasonable expectation of success for introducing the claimed constructs to cells. The rejections based on at least Hallahan I in view of Teng, Neta and Vile are reversed.

Hallahan II in view of Teng and Vile

Examiner argues that Hallahan II disclose "clinical trials in which TNF was administered to patients prior to radiation treatment" (Examiner's Answer, p. 11). Examiner admits that the reference does not teach transfecting a cell with a construct comprising the TNF gene and contacting the cell with ionizing radiation whereby the gene is expressed and the cancer is treated or nontumor cells are protected. To overcome the lack of teaching to transfect a cell with TNF,

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USPQ2d 1529, 1531 (Fed. Cir. 1988). Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure. Id."

examiner cites Teng and Vile. Examiner also emphasizes that Hallahan II suggests gene therapy.

Regarding the suggestion by Hallahan II to employ gene therapy, this is the extent of the disclosure: "... phase I trials of TNF gene therapy localized to tumors in combination with radiation are warranted." See last two lines of document. We are provided no other information. The rest of the document is vague at best about any transfection procedure. In our view, while Hallahan II would appear to suggest conducting gene therapy in the future, it lacks the requisite information to enable one to conduct a transfection procedure. Accordingly, by itself, Hallahan II carries little weight as evidence in determining whether the claimed transfection procedures would have been obvious to one of ordinary skill in the art.

Regarding Teng and Vile, examiner (Examiner's Answer, p. 11) states that:

> Teng et al. disclose experiments in which murine tumor cells were transfected with the human TNF gene under control of the CMV intermediate early promoter, then implanted into nude mice (entire document). Teng et al. show that transfected tumor cell lines which produce moderate levels of TNF grow more slowly than non-transfected cell lines when implanted, and that this level of TNF production does not cause serious weight loss (e.g. Table 1). Vile et al. teach a method for transfecting tumor cells and surrounding normal cells *in vivo* by direct injection of DNA into a tumor (pp. 965-966).

As a result, examiner (Examiner's Answer, pp. 11-12) concludes:

> It would have been obvious to one of ordinary skill in the art at the time the invention was made to transfect tumor cells with a gene encoding TNF prior to radiation therapy, as suggested by Hallahan et al. It would have been obvious to use the CMV/TNF construct of Teng et al., transfecting by direct

injection as taught by Vile et al. There would have been a reasonable expectation of success, given the known radiosensitizing and radioprotecting effects of TNF as taught by Hallahan et al., the demonstrated efficacy of the construct of Teng et al., and the expectation that both tumor and normal cells would be transfected by injection as taught by Vile et al. Thus, the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Notwithstanding examiner's conclusion, for the following reasons, we find that examiner has not met his initial burden of establishing a prima facie case of obviousness. In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992).

Examiner admits that Hallahan II does not explicitly teach transfection but relies on Teng and Vile to make the case that transfection is an alternative to Hallahan II's adding of TNF to a medium containing cells. Even if we were to find that Hallahan II with Teng and Vile would have suggested to those of ordinary skill in the art that transfection and addition of TNF to cells are equivalent alternatives, to establish the prima facie case of obviousness, the prior art would have to also reveal that, in so including the construct, those of ordinary skill would have had a reasonable expectation of success in obtaining a transfected cell able to treat a human cancer patient (claim 1), sensitize a cell to the effects of ionizing radiation (claim 12), radioprotect a cell from the effects of ionizing radiation (claims 18 and 26), and inhibit the growth of a tumor (claim 35). "Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure." In re Vaeck, 947 F. 2d 488, 493

20 USPQ2d 1438, 1442 (Fed. Cir. 1991).[6] The burden rests on the examiner to support the prima facie case of obviousness with a further showing that in introducing the constructs to the cells there would have been a reasonable expectation of success in obtaining the claimed effects. Here that has not been done.

Although examiner makes the case that each of the claimed elements are known in the art, examiner does not show that the behavior of the genes in constructs introduced to cells behave the same as genes added to a medium containing the cells. In fact, examiner (Examiner's Answer, p. 11) states that Teng shows "that transfected tumor cell lines which produce moderate levels of TNF grow more slowly than non-transfected cell lines when implanted." This suggests to us that the behavior of transfected and nontransfected cells with radioprotecting/radiosensitizing genes is not the same and therefore the ultimate result is a matter of speculation. Accordingly, we do not find that examiner has established a reasonable expectation of success for introducing the claimed constructs to cells. The rejections based on at least Hallahan II in view of Teng and Vile are reversed.

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[6] "Where claimed subject matter has been rejected as obvious in view of a combination of prior art references, a proper analysis under § 103 requires, inter alia, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. See In re Dow Chemical Co., 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure. Id."

VACATE AND REMAND

Examiner's prima facie case focuses on the obviousness of transfecting tumor cells with a gene such as the TNF gene. However, not all the claims are directed to transfection. Claims 29 and 30 are directed to a pharmaceutical composition, not transfection. Examiner does not explain how the prior art renders this composition obvious.

Examiner does make the comment that "Teng et al. disclose experiments in which murine tumor cells were transfected with the human TNF gene under control of the CMV intermediate early promoter, then implanted into nude mice (entire document)." (Examiner's Answer, p. 6). Examiner does not direct us to a particular passage but, from our review of the document, the only mention of using a promoter appears on page 3535, column 2, fourth full paragraph: "The mammalian expression vector pCMVIE-AK1-DHFR with a human genomic clone of the TNF gene inserted in the *Bgl* II site was kindly provided by ..." We presume this is the disclosure examiner is referring to, although that is unclear. If so, examiner has not explained how this disclosure renders obvious the invention set forth in claims 29 and 30. Claim 29 is directed to a gene construct comprising a constitutive promoter but dispersed in a pharmacologically acceptable carrier. Claim 30 further limits claim 29 by packaging the construct in a virion or virus particle. These other limitations are not addressed. Examiner has not addressed all the limitations in these claims and, accordingly, examiner's position is insufficient.

The issue for our review is whether the inventions of claims 29 and 30 are properly rejectable under § 103 as being unpatentable over the cited prior art combination. After careful review of the record, we find the examiner's position raised in this appeal is not amenable to a meaningful review. Under the present circumstances, the position put forward by the examiner in support of the rejections is insufficient for the reasons supra. Since the Board serves as a board of review, not a de novo examination tribunal (35 U.S.C. § 6(b)), it is necessary that we understand examiner's position and that that position be thoroughly presented before we make that review. Accordingly, we vacate the rejections as they apply to these claims and remand the application to the examiner so that the issue of obviousness can be reconsidered in light of our discussion and, if reinstituted, supported with proper grounds.

For the foregoing reasons, we vacate the rejections under § 103 as they apply to claims 29 and 30 and remand to give the examiner an opportunity to consider the issues discussed herein and take appropriate action not inconsistent with the views expressed herein. We emphasize that we vacate examiner's rejections as to claims 29 and 30. This means that the instant rejections as they apply to claims 29 and 30 no longer exist. See Ex parte Zambrano, 58 USPQ2d 1312, 1313 (Bd. Pat. App. & Int. 2000).

The rejection of claims 1, 3, 6, 8-14, 17-22 and 26-30 and 35 under 35 U.S.C. § 112, first paragraph, is reversed. The rejections of claims 1-3, 6,

8-14, 17-22 and 26-28 and 31-36 under 35 U.S.C. § 103 are reversed. The rejections of claims 29 and 30 under 35 U.S.C. § 103 are vacated.

This application, by virtue of its "special" status, requires an immediate action. MPEP § 708.01 (7th Ed., July 1998). It is important that the Board be informed promptly of any action affecting the appeal in this case.

REVERSED-IN-PART, VACATED-IN-PART, AND REMANDED

SHERMAN D. WINTERS)
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